**Phenylketonuria (PKU)**

#### What is phenylketonuria (PKU)?

Phenylketonuria (PKU) is an inherited disorder of metabolism that causes an increase in the blood of a chemical known as phenylalanine. Phenylalanine is an amino acid that comes from a person's diet and is used by the body to make proteins. Phenylalanine is found in all food proteins and in some artificial sweeteners. Without dietary treatment, phenylalanine can build up to harmful levels in the body, causing mental retardation and other serious problems.

Gene alterations (mutations) in the PAH gene cause PKU. Mutations in the PAH gene cause low levels of an enzyme called phenylalanine hydroxylase. This enzyme normally converts Phe to another amino acid, tyrosine. Without this enzyme, Phe accumulates in the blood and body tissues. Excess Phe is toxic to the central nervous system and causes the severe problems normally associated with PKU. When left untreated, PKU patients who consume too much Phe are at risk of severe neurological complications, including IQ loss, memory loss, concentration problems, mood disorders, and in some cases, severe mental retardation.

Women who have high levels of phenylalanine during pregnancy are at high risk for having babies born with mental retardation, heart problems, small head size (microcephaly) and developmental delay. This is because the babies are exposed to their mother's very high levels of phenylalanine before they are born.

CAUSE AND INCIDENCE OF PKU

Classical PKU affects between 1 in 10,000 and 1 in 20,000 depending on the country of origin. The incidence varies widely in different human populations from 1 in 4,500 births among the population of Ireland[3] to fewer than one in 100,000 births among the population of Finland.[4] Even higher levels have been reported in the Eastern Mediterranean region (1 in 4,000 in Turkey and 1 in 3,627 in the Islamic Republic of Iran).[5] Poland and the Czech Republic also reportedly have high incidence rates. In the US the incidence rate appears to be between 1 in 10,000 to 1 in 20,000 for Caucasians and Asians. In the USA there are roughly 9000 persons with PKU since Newborn Screening (NBS) initiated (est. 210 live births per year X 43.5 years [1965]) Approx. 5500 more persons with PKU who predated NBS are in dependent living homes/institutions (avg live span 75 years-31.5 years pre-1965 X est. 185 live births per year). Total: 14,500 persons in the US living with PKU. The incidence among African Americans is much less. There is no difference in frequency of occurrence between males and females .[6]

SYMPTOMS AND DIAGNOSIS

Newborns affected by PKU usually do not show any signs of the disease at birth. But within the first few weeks of life they begin to show neurologic disturbances such as epilepsy. Children suffering from undiagnosed PKU also may have a "musty or mousy" odor of skin, hair, sweat and urine (due to phenylacetate accumulation). It has been shown that almost 90% of affected people have light coloration such as blond hair and blue eyes. Signs also include skeletal changes such as a small head, short stature, and flat feet. PKU sufferers may also exhibit skin disorder ( eczema). tremors, jerking movements of the arms or legs, and unusual hand posturing. Hyperactivity, EEG abnormalities,  seizures, and severe learning disabilities are major clinical problems later in life. If left untreated, the child is likely to experience behavior problems and developmental delays. Severe brain problems may occur such as mental retardation.

The initiation of screening in the mid-1960’s throughout the US of all newborns has resulted in the early identification and treatment of PKU affected children with very successful results. The several hundred babies diagnosed each year and placed on diet are growing up normally.

TREATMENT

Newborn screening allows early identification and early implementation of treatment. [The goal of PKU treatment is to maintain the blood level of Phe between 2 and 6 mg/dl[9]](https://southeastgenetics.org/ngp/guidelines_pku.php). Some Phe is needed for normal growth. This requires a diet that has some Phe but in much lower amounts than normal. High protein foods such as: meat, fish, poultry, eggs, cheese, milk, dried beans, and peas are avoided. Instead, measured amounts of cereals, starches, fruits, and vegetables, along with a milk substitute are usually recommended. These foods are allowed in quantities that suit the individual child's tolerance for Phe; some can have fairly liberal diets and still maintain good control of blood phe, while others must have a very strict diet. A synthetic, Phe free formula is used as a nutritional substitute for the eliminated foods. Formulas are available for all age groups.

Previously, PKU affected individuals were allowed to go off diet after approximately 6 to 12 years of age. Now treatment is for life, in order to promote maximal development and cognitive abilities. Trying to reinstitute the PKU diet after a period of 'relaxation' to a regular diet, has been difficult for many individuals. Periodic Phe blood level measurement, and the guidance of a nutritionist and other members of the health care team, allow individuals and families to work toward consistently maintaining the blood level in the desirable range.

In just the past few years two new products have become available for persons with PKU. Kuvan, a prescription drug, causes residual enzyme activity to work harder to reduce blood Phe levels and has been effective in reducing blook Phe levels in some people with PKU. Another new product with limited application are large neutral amino acides (LNAA's) which work by blocking Phe uptake through the digestive tract.

Modified from the following source:

“Learning About Phenylketonuria.” *National Human Genome Research Institute (NHGRI)*, https://www.genome.gov/25020037/learning-about-phenylketonuria/.

“NPKUA ≫ Education ≫ About PKU.” *NPKUA ≫ Education ≫ About PKU*, http://npkua.org/education/about-pku.

**Melanoma**

#### What is Melanoma?

Cancer starts when cells in the body begin to grow out of control. Cells in nearly any part of the body can become cancer, and can then spread to other areas of the body. Melanoma is a cancer that usually starts in a certain type of skin cell called melanocytes, which are the pigment (melanin) producing cells in the skin. Other names for this cancer include *malignant melanoma* and*cutaneous melanoma*. Most melanoma cells still make melanin, so melanoma tumors are usually brown or black. But some melanomas do not make melanin and can appear pink, tan, or even white.

Melanomas can develop anywhere on the skin, but they are more likely to start on the trunk (chest and back) in men and on the legs in women. The neck and face are other common sites.

Having darkly pigmented skin lowers your risk of melanoma at these more common sites, but anyone can get melanoma on the palms of the hands, soles of the feet, and under the nails. Melanomas in these areas make up a much larger portion of melanomas in African Americans than in whites.

Melanoma is much less common than basal cell and squamous cell skin cancers. But melanoma is more dangerous because it’s much more likely to spread to other parts of the body if not caught early.

CAUSE AND INCIDENCE

Many [risk factors](http://www.cancer.org/ssLINK/melanoma-skin-cancer-risk-factors" \t "_top) for melanoma have been found, but it’s not always clear exactly how they might cause cancer.

For example, while most moles never turn into a melanoma, some do. Researchers have found some gene changes inside mole cells that may cause them to become melanoma cells. But it’s still not known exactly why some moles become cancerous while most don’t.

DNA is the chemical in each of our cells that makes up our genes, which control how our cells function. We usually look like our parents because they are the source of our DNA. But DNA affects more than just how we look.

Some genes control when our cells grow, divide into new cells, and die:

* Genes that help cells grow, divide, and stay alive are called *oncogenes*.
* Genes that keep cell growth in check or cause cells to die at the right time are called *tumor suppressor genes*.

Cancers can be caused by DNA changes that turn on oncogenes or turn off tumor suppressor genes. Changes in several different genes are usually needed for a cell to become a cancer cell.

Ultraviolet (UV) rays are clearly a major cause of melanoma. UV rays can damage the DNA in skin cells. Sometimes this damage affects certain genes that control how skin cells grow and divide. If these genes no longer work properly, the affected cells may become cancer cells.

Most UV rays come from sunlight, but some can come from man-made sources such as tanning beds. Usually it’s not clear exactly when the DNA damage from UV exposure occurs. Some of the damage may take place in the few years before the cancer appears. But much of it may be from exposures that happened many years earlier. Children and young adults often get a lot of intense sun exposure that might not result in cancer until many years or even decades later.

Most of the gene changes commonly seen in melanoma cells are not inherited. They are more likely the result of damage caused by sunlight. In some people, such as those with xeroderma pigmentosum (XP), the skin cells are not as able to repair damaged DNA. These people are more likely to develop melanoma.

Some melanomas occur in parts of the body that are rarely exposed to sunlight. These melanomas often have different gene changes than those in melanomas that develop in sun-exposed areas.

When melanomas run in families, gene changes (mutations) that greatly increase the risk of melanoma are often passed from one generation to the next. Familial (inherited) melanomas most often have changes in tumor suppressor genes such as *CDKN2A* (also known as *p16*) and *CDK4* that prevent them from doing their normal job of controlling cell growth. This could eventually lead to cancer.

Many other gene changes have been found in melanoma cells as well. Some of these have proven to be good targets for drugs to help treat this disease. For example, about half of all melanomas have a change in the *BRAF* oncogene that helps drive their growth. This change is not inherited. It seems to occur during the development of the melanoma. Several drugs that specifically target cells with this gene change are now used to treat these melanomas

Modified from:

“Signs and Symptoms of Melanoma Skin Cancer.” *Signs and Symptoms of Melanoma Skin Cancer*, http://www.cancer.org/cancer/skincancer-melanoma/detailedguide/melanoma-skin-cancer-signs-and-symptoms.

**Albinism**

#### What is Albinism?

Albinism is an inherited genetic condition that reduces the amount of melanin pigment formed in the **skin, hair and/or eyes**. Albinism occurs in all racial and ethnic groups throughout the world. In the U.S., approximately one in 18,000 to 20,000 people has some type of albinism. In other parts of the world, the occurrence can be as high as one in 3,000. Most children with albinism are born to parents who have normal hair and eye color for their ethnic backgrounds.

Researchers have identified multiple types of oculocutaneous albinism, which are distinguished by their specific skin, hair, and eye color changes and by their genetic cause. Oculocutaneous albinismtype 1 is characterized by white hair, very pale skin, and light-colored irises. Type 2 is typically less severe than type 1; the skin is usually a creamy white color and hair may be light yellow, blond, or light brown. Type 3 includes a form of albinism called rufous oculocutaneous albinism, which usually affects dark-skinned people. Affected individuals have reddish-brown skin, ginger or red hair, and hazel or brown irises. Type 3 is often associated with milder vision abnormalities than the other forms of oculocutaneous albinism. Type 4 has signs and symptoms similar to those seen with type 2.

## Types of Albinism

While most people with albinism have very light skin and hair, levels of pigmentation can vary depending on one’s type of albinism. Oculocutaneous (pronounced ock-you-low-kew-TAIN-ee-us) albinism (OCA) involves the eyes, hair and skin.

Ocular albinism (OA), which is much less common, involves only the eyes, while skin and hair may appear similar or slightly lighter than that of other family members.

Over the years, researchers have used various systems for classifying oculocutaneous albinism. In general, these systems contrasted types of albinism having almost no pigmentation with types having slight pigmentation. In less pigmented types of albinism, hair and skin are cream-colored and vision is often in the range of 20/200. In types with slight pigmentation, hair appears more yellow or has a reddish tinge and vision may be better.

Oculocutaneous albinism can result from mutations in several genes, including [*TYR*](https://ghr.nlm.nih.gov/gene/TYR), [*OCA2*](https://ghr.nlm.nih.gov/gene/OCA2), [*TYRP1*](https://ghr.nlm.nih.gov/gene/TYRP1), and [*SLC45A2*](https://ghr.nlm.nih.gov/gene/SLC45A2). Changes in the *TYR* gene cause type 1; mutations in the *OCA2* gene are responsible for type 2; *TYRP1* mutations cause type 3; and changes in the *SLC45A2* gene result in type 4. Mutations in additional genes likely underlie the other forms of this disorder. The genes associated with oculocutaneous albinism are involved in producing a pigment called [melanin](https://ghr.nlm.nih.gov/art/large/melanocyte.jpeg), which is the substance that gives [skin](https://ghr.nlm.nih.gov/art/large/skin-anatomy-with-melanocyte.jpeg), hair, and eyes their color. In the retina, melanin also plays a role in normal vision. Mutations in any of these genes disrupt the ability of cells to make melanin, which reduces pigmentation in the skin, hair, and eyes. A lack of melanin in the retina leads to the vision problems characteristic of oculocutaneous albinism.

Alterations in the [*MC1R*](https://ghr.nlm.nih.gov/gene/MC1R) gene can change the appearance of people with oculocutaneous albinism type 2. This gene helps regulate melanin production and is responsible for some normal variation in pigmentation. People with genetic changes in both the *OCA2* and *MC1R* genes have many of the usual features of oculocutaneous albinism type 2, including light-colored eyes and vision problems; however, they typically have red hair instead of the usual yellow, blond, or light brown hair seen with this condition.

## Vision Considerations

People with albinism have vision problems that are not correctable with eyeglasses, and many have low vision. It’s the abnormal development of the retina and abnormal patterns of nerve connections between the eye and the brain that cause vision problems. The presence of these eye problems defines the diagnosis of albinism.

A common myth is that people with albinism have red eyes. Although lighting conditions can allow the blood vessels at the back of the eye to be seen, which can cause the eyes to look reddish or violet, most people with albinism have blue eyes, and some have hazel or brown eyes. There are different types of albinism and the amount of pigment in the eyes varies; however, vision problems are associated with albinism.

The degree of impairment varies with the different types of albinism. Although people with albinism may be considered “legally blind” with a corrected visual acuity of 20/200 or worse, most learn to use their vision in a variety of ways and are able to perform innumerable activities such as reading, riding a bike or fishing. Some have sufficient vision to drive a car.

## Dermatological Considerations

Affected individuals typically have very fair skin and white or light-colored hair. Long-term sun exposure greatly increases the risk of skin damage and skin cancers, including an aggressive form of skin cancer called [melanoma](https://ghr.nlm.nih.gov/art/large/melanoma-skin.jpeg), in people with this condition. Because most people with albinism have fair complexions, it’s important to avoid sun damage to the skin and eyes by taking precautions such as wearing sunscreen or sunblock, hats, sunglasses and sun-protective clothing.

## Frequency

Overall, an estimated 1 in 20,000 people worldwide are born with oculocutaneous albinism. The condition affects people in many ethnic groups and geographical regions. Types 1 and 2 are the most common forms of this condition; types 3 and 4 are less common. Type 2 occurs more frequently in African Americans, some Native American groups, and people from sub-Saharan Africa. Type 3, specifically rufous oculocutaneous albinism, has been described primarily in people from southern Africa. Studies suggest that type 4 occurs more frequently in the Japanese and Korean populations than in people from other parts of the world.

**Modified from:**

“Oculocutaneous Albinism - Genetics Home Reference.” *U.S National Library of Medicine*, U.S. National Library of Medicine, https://ghr.nlm.nih.gov/condition/oculocutaneous-albinism#statistics.

**Hemophilia**

#### What is Hemophilia?

Hemophilia is a bleeding disorder that slows the [blood clotting process](https://ghr.nlm.nih.gov/art/large/blood-clot-formation.jpeg). People with this condition experience prolonged bleeding or oozing following an injury, surgery, or having a tooth pulled. In severe cases of hemophilia, continuous bleeding occurs after minor trauma or even in the absence of injury (spontaneous bleeding). Serious complications can result from bleeding into the joints, muscles, brain, or other internal organs. Milder forms of hemophilia do not necessarily involve spontaneous bleeding, and the condition may not become apparent until abnormal bleeding occurs following surgery or a serious injury.

The major types of this condition are hemophilia A (also known as classic hemophilia or factor VIII deficiency) and hemophilia B (also known as Christmas disease or factor IX deficiency). Although the two types have very similar signs and symptoms, they are caused by mutations in different genes. People with an unusual form of hemophilia B, known as hemophilia B Leyden, experience episodes of excessive bleeding in childhood but have few bleeding problems after puberty.

Changes in the [*F8*](https://ghr.nlm.nih.gov/gene/F8) gene are responsible for hemophilia A, while mutations in the [*F9*](https://ghr.nlm.nih.gov/gene/F9) gene causehemophilia B. The *F8* gene provides instructions for making a protein called coagulation factor VIII. A related protein, coagulation factor IX, is produced from the *F9* gene. Coagulation factors are proteins that work together in the [blood clotting process](https://ghr.nlm.nih.gov/art/large/blood-clot-formation.jpeg). After an injury, blood clots protect the body by sealing off damaged blood vessels and preventing excessive blood loss.

Mutations in the *F8* or *F9* gene lead to the production of an abnormal version of coagulation factor VIII or coagulation factor IX, or reduce the amount of one of these proteins. The altered or missing protein [cannot participate effectively in the blood clotting process](https://ghr.nlm.nih.gov/art/large/impaired-blood-clotting-in-hemophilia.jpeg). As a result, blood clots cannot form properly in response to injury. These problems with blood clotting lead to continuous bleeding that can be difficult to control. The mutations that cause severe hemophilia almost completely eliminate the activity of coagulation factor VIII or coagulation factor IX. The mutations responsible for mild and moderate hemophilia reduce but do not eliminate the activity of one of these proteins.

The two major forms of hemophilia occur much more commonly in males than in females. Hemophilia A is the most common type of the condition; 1 in 4,000 to 1 in 5,000 males worldwide are born with this disorder. Hemophilia B occurs in approximately 1 in 20,000 newborn males worldwide.

### Symptoms

People with hemophilia A often, bleed longer than other people. Bleeds can occur internally, into joints and muscles, or externally, from minor cuts, dental procedures or trauma. How frequently a person bleeds and the severity of those bleeds depends on how much FVIII is in the plasma, the straw-colored fluid portion of blood.

Normal plasma levels of FVIII range from 50% to 150%. Levels below 50%, or half of what is needed to form a clot, determine a person’s symptoms.

* **Mild hemophilia A-  6% up to 49% of FVIII in the blood.** People with mild hemophilia Agenerally experience bleeding only after serious injury, trauma or surgery. In many cases, mild hemophilia is not diagnosed until an injury, surgery or tooth extraction results in prolonged bleeding. The first episode may not occur until adulthood. Women with mild hemophilia often experience menorrhagia, heavy menstrual periods, and can hemorrhage after childbirth.7
* **Moderate hemophilia A. 1% up to 5% of FVIII in the blood.** People with moderate hemophilia A  tend to have bleeding episodes after injuries. Bleeds that occur without obvious cause are called spontaneous bleeding episodes.
* **Severe hemophilia A.  <1% of FVIII in the blood.**People with severe hemophilia A experience bleeding following an injury and may have frequent spontaneous bleeding episodes, often into their joints and muscles.

### Diagnosis

The best place for patients with hemophilia to be diagnosed and treated is at one of the federally-funded hemophilia treatment centers (HTCs) that are spread throughout the country. HTCs provide comprehensive care from skilled hematologists and other professional staff, including nurses, physical therapists, social workers and sometimes dentists, dieticians and other healthcare providers.

A medical health history is important to help determine if other relatives have been diagnosed with a bleeding disorder or have experienced symptoms. Tests that evaluate clotting time and a patient’s ability to form a clot may be ordered. A clotting factor test, called an assay, will determine the type of hemophilia and its severity.

### Treatment

The main medication to treat hemophilia A is concentrated FVIII product, called clotting factor or simply factor. Recombinant factor products, which are are developed in a lab through the use of DNA technology, , preclude the use of human-derived pools of donor-sourced plasma. And while plasma-derived FVIII  products are still available, approximately 75% of the hemophilia community takes a recombinant FVIII product.

These factor therapies are infused intravenously through a vein in the arm or a port in the chest. The Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation encourages the use of recombinant clotting factor products because they are safer. Your doctor or your HTC will help you decide which is right for you.

Patients with severe hemophilia may be on a routine treatment regimen, called prophylaxis, to maintain enough clotting factor in their bloodstream to prevent bleeds. MASAC recommends prophylaxis as optimal therapy for children with severe hemophilia A.

**Modified from:**

@NHF\_Hemophilia. “Hemophilia A.” *National Hemophilia Foundation*, 15 July 2015, https://www.hemophilia.org/bleeding-disorders/types-of-bleeding-disorders/hemophilia-a.